(1)-1 Rheumatoid Arthritis

VX-745 Vertex Pharmaceuticals

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VX-745, a lead anti-inflammatory candidate, small-molecule inhibitor of mitogen-activated protein kinase (MAPK), is under development by Vertex Pharmaceuticals Inc in association with Kissei Pharmaceutical Co Ltd for the potential treatment of rheumatoid arthritis (RA) [214928]. VX-745 was introduced by Vertex as a potential anti-inflammatory drug for the treatment of RA in a pilot phase II trial initiated in November 1999 [346067]. In June 2000, phase II trials were still ongoing [371819] and in January 2001, Vertex initiated a randomized, double-blind, placebo-controlled phase II trial in adult patients with RA, with the objective of evaluating clinical response rates, self-reported patient health assessments and pharmacodynamic markers of drug activity [395083].

During the 33rd Annual Meeting of the American Chemical Society in May 2000, VX-745 was reported to be active against several isotypes of p38 MAPK, including p38α, p38β and p38γ [368149]. The targeting of p38 MAPK by VX-745 was associated with the suppression of the release of inflammatory mediators, including interleukin (IL)-1β and tumor necrosis factor (TNF)α, known to be implicated in exacerbating the pathophysiology of RA [273648], [368149], [371548], [372054], [408713].

Originator Vertex Pharmaceuticals Inc

Licensee Kissei Pharmaceutical Co Ltd

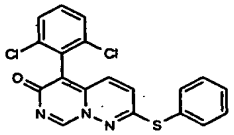
Status Phase II Clinical

Indication Rheumatoid arthritis, Inflammation, Neurological disease

Action p38 MAP kinase inhibitor

Synonyms & Analogs VK-19911, VK-21931, p38 MAP kinase inhibitors (Vertex)

CAS 6H-Pyrimido[1,6-*b*]pyridazin-6-one, 5-(2,6-dichlorophenyl)-2-(phenylthio)-
Registry No: 209409-98-3



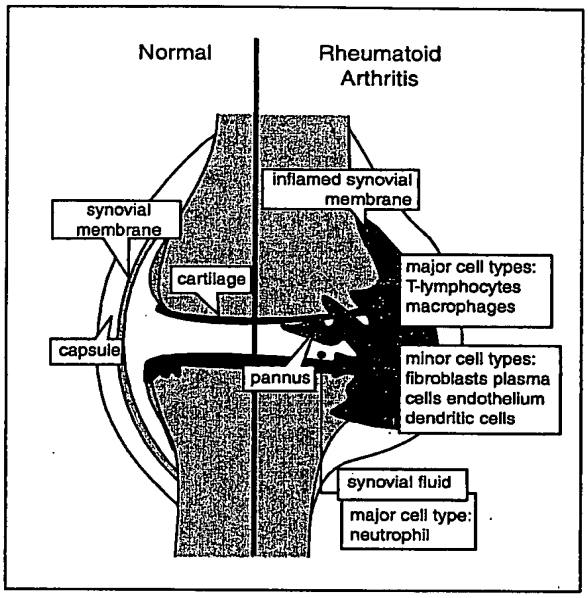
Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease [208892], [248952], [265991], which particularly affects the synovial articulating joints, and is characterized by the infiltration of immunocompetent cells and the formation of pannus tissue that causes the degradation of articular cartilage and subchondral bone (*See* the diagrammatic representation below in Figure 1) [225361]. Despite the fact that the etiology of RA remains largely obscure, recent discoveries and research efforts are providing insight into the underlying molecular mechanisms involved in regulating the progression of RA *in vitro* [40585], [172466], [352592] and *in vivo* [110120], [227586], [265856], [310667], [407697].

The expression and regulation of downstream mediators of inflammation and joint damage in RA include inflammatory cytokines, of which interleukin (IL)-1β [70702], [162758], [233807], [263691] and tumor necrosis factor (TNF)α [251779], [254161], [254164], [254176], [282339], [282369] are reported to promote cartilage degradation, amplify the release of other inflammatory mediators and upregulate the expression of vascular adhesion molecules. This allows the infiltration of neutrophils and lymphocytes, thereby exacerbating the condition of the inflamed joint [208892], [225361], [227586], [407697].

Many extracellular stimuli, including pro-inflammatory cytokines and other inflammatory mediators, elicit specific cellular responses through the activation of mitogen-activated protein kinase (MAPK) signaling pathways [254172], [266863], [296010], [296038]. MAPKs are proline-targeted serine-threonine kinases that transduce environmental stimuli to the nucleus and they themselves are activated by upstream MAPK kinases (MAPKKs) on both threonine and tyrosine residues within an 'activation loop' [280369], [296038]. Once activated, MAPKs can phosphorylate and activate other kinases or nuclear proteins, including potential transcription factors and substrates. The novel mammalian reactivating protein kinase (p38/RK) MAPKs are stress-activated protein kinases (SAPK) that mediate responses to cellular stresses such as UV irradiation, osmotic imbalance, heat shock, DNA damage, bacterial products, such as lipopolysaccharide (LPS), and inflammatory signals [296038]. Furthermore, inflammatory mediators, such as cytokines, activate p38/RK MAPK pathway in several cell types [266863], [296038]. Of note, p38/RK MAPK has been recently implicated in regulating pro-inflammatory cytokine biosynthesis [225706], [225707], [254575], [257155], [260568], [363873] and transcription [285724], [366385]. Recently, the p38 MAPK signal transduction pathway has emerged as a target for the development of a therapeutic strategy in pathophysiological conditions such as RA [210214], [257153], [348258], [355006], [377246], [379930], [400737], [411102]. Therefore, targeting this enzyme and the downstream inflammatory pathways that MAPK regulates has been the focus of efforts at Vertex Pharmaceuticals Inc to create a drug that selectively interferes with, and blocks, the inflammatory potential of p38 MAPK [273428], [307144].

Figure 1. Diagramatic representation of the effects of RA on a synovial joint.



Synthesis and SAR

In November 1996, Vertex reported the three-dimensional X-ray crystallographic structure of p38 MAPK [224121], [338958], and thereby benefited from this high-resolution (2.3 Å) crystalline structure of the enzyme to design therapeutic drugs that target and block inflammatory mediators regulated by p38 MAPK. The structure revealed the active site of p38 MAPK and also the shape and orientation of the binding loop for ATP, a cofactor molecule [224121], [246805], [268553], [303458], [321050]. Once p38 MAPK is activated, a gate uncovers the active site allowing optimum and efficient binding of ATP, thereby leading to subsequent phosphorylation and activation of the enzyme. The geometry of p38 MAPK, subsequently, allowed the screening of various inhibitors that bind p38 MAPK and block the active site gate [308835], [314282], [320920]. An X-ray structure of the lead compound, VK-19911, was developed and its binding to p38 MAPK studied [262571], [369960]. The compound binds to the ATP site and the Thr^{106} residue was found to rotate, thus allowing the binding of the inhibitor [369960]. VK-19911 was modeled as a p38 MAPK inhibitor, with similar binding kinetics to phosphorylated and unphosphorylated forms of p38 MAPK through binding to the ATP pocket, and has similar properties to SB-203580 (SmithKline Beecham) [268556], [269032], [299095]. Further development led to VK-21931 and SAR built around this small molecule generated VX-745. No data are currently available on the affinity of the compound for the enzyme in comparison with other pyridinylimidazole derivatives [242365], [257155], [268556], [285724], [299095], [314282], [352592], [363873].

Pharmacology

Following the discovery of the crystal structure of p38 MAPK [224121], Vertex and Kissei have collaborated to develop novel pharmacological drugs to treat inflammatory and neurological disease [262571], [273428], [291135], [307144]. The agreement focuses on the design and development of inhibitors of p38 MAPK, a human enzyme involved in the onset and progression of inflammation and programmed cell death [225707], [254172], [285724], [296010], [296038]. VX-745 was identified as such a novel inhibitor of p38 MAPK and the implicated downstream inflammatory pathways [262571], [291135], [372054], [372943].

p38 MAPK is a specific enzyme that regulates the production of IL-1 [266863], [393037], IL-2 [260568], IL-6 [225706], TNFα [254575], [296010], chemokines [366385] and nitric oxide (NO) [296010], as part of acute and chronic inflammatory responses [222881], [225707], [257155], [348258]. In preclinical studies, VX-745 blocked the disease progression in animal models of RA and stroke [291135]. The rapid development of VX-745 from discovery to phase I clinical trials reflects this novel approach adopted to counteract and suppress the inflammatory process [262571], [291135]. As such, the phase I, randomized blinded clinical trial launched in 1999 was designed to test the pharmacokinetics and tolerability of VX-745 in escalating single doses in healthy volunteers [317656] and led to the initiation of phase II trial in patients with RA [346067].

In vitro, VX-745 was selective for p38 MAPK compared to a large panel of kinases ($IC_{50} \geq 20$ μM). VX-745 selectively inhibited p38α MAPK ($IC_{50} = 10$ nM), p38β MAPK ($IC_{50} = 220$ nM) [368149], but not p38γ MAPK ($IC_{50} \geq 20$ μM) [368149]. In addition, cell data for VX-745 in a human peripheral blood mononuclear cell (PBMC) assay provided IC_{50} values of 56 and 52 nM [408713] for IL-1β and TNFα, respectively, and VX-745 blocked IL-6 and IL-8 production induced by IL-1 and TNFα, and cyclooxygenase (COX)-2 synthesis mediated by LPS and IL-1β [408713]. In a human whole blood assay, IC_{50} values were 152 and 177 nM for IL-1β and TNFα inhibition, respectively [368149], [372054].

In the classical cartilage-induced arthritis model, VX-745 exhibited a dose-responsive decrease in severity score [369960]. Furthermore, 33.1% suppression of paw inflammation was observed with VX-745 (10 mg/kg bid), which was equivalent to maximum effect using prednisolone [368149], [372054], [372943]. VX-745 was also effective against adjuvant-induced arthritis (AA) in the rat, with an ED_{50} value of 5 mg/kg bid, indicated by measuring ankle joint diameter; the efficacy at this dose was also equal to the maximal efficacy observed with prednisolone [368149]. Histological scores for VX-745 in AA rat were 93% inhibition of bone resorption and 56% inhibition of inflammation [368149]. Improvement in bone resorption seems to be a hallmark of p38 inhibitors [368149], [369960], [371548], [374146].

Metabolism
The pharmacological actions of VX-745 arise from its ability to irreversibly compete with ATP in the active binding site of p38 MAPK, thereby rendering the enzyme inactive [273428], [291135], [346067], [372054], [372943]. VX-745 is insoluble in water, but by using different vehicles, it has been reported to be bioavailable [372054], [372943]. Oral pharmacokinetic studies in the rat (n = 3) demonstrated a bioavailability of 56% at 40 mg/kg with a t of 4.5 h, using an isopropanol vehicle [369960], [372054], [372943]. Detailed data on the metabolism of VX-745, however, are not currently available.

Toxicity
No toxicity data are currently available.

Clinical Development
Vertex initiated its p38 MAPK discovery program in 1996 [224121], leveraging proprietary structural information of the p38 enzyme and performing cluster-based screening of compound libraries to generate potential drug leads [291135]. In July 1998, Vertex and Kissei Pharmaceuticals announced that they had selected VX-745 as a lead drug development candidate [291135]. Following successful completion of preclinical studies, both companies began planning for clinical development of VX-745 in 1999 [291135], [317656].

Phase I
In March 1999, the initiation of a phase I clinical trial with VX-745 was announced [262571], [291135], [317656]. The phase I randomized, blinded clinical trial was designed to assess the pharmacokinetics and tolerability of VX-745 in escalating single doses in healthy volunteers. As part of the study, researchers analyzed blood samples to determine the ability of different doses of VX-745 to inhibit experimentally-induced TNFα production using specific biochemical assays [317656]. Following completion of the study, Vertex conducted additional single and multidose trials of VX-745 later in the same year [317656].

Phase II
In November 1999, Vertex announced that it had begun an exploratory phase II trial of VX-745 to provide further information about its pharmacodynamic activity and potential for the treatment of RA, and help design larger studies aimed at evaluating the safety and efficacy of the drug [346067], [371819], [372054], [372943]. In June 2000, phase II trials were ongoing [371819]. Commencing January 2001, a dose-ranging multicenter, randomized, double-blind, placebo-controlled trial tested two different doses of VX-745 in approximately 135 adult RA patients [395083]. The trial was designed to explore the clinical activity and tolerability of escalating doses of VX-745 when given as a monotherapy for 3 months. The trial enrolled patients who had active RA and were not responding adequately to their current therapy. The trial, furthermore, evaluated objective clinical response rates, self-reported patient health assessments, and pharmacodynamic markers of drug activity [395083]. However, no published data from clinical trials are currently available.

Side Effects and Contraindications
No data are currently available.

Current Opinion
Since the discovery of the p38 MAPK pathway as a regulatory mechanism controlling the inflammatory mediators [291135], [348258], [352592], [386727], [400737], efforts have concentrated on targeting this pathway, with potent selective inhibitors, which lack side effects, contraindications or toxicity. RA is one of the commonest human autoimmune diseases [208892], [225361], [265991], and of its numerous clinical features, perhaps inflammatory cytokines, such as IL-1 and TNFα, are the most crucial mediators that drive a cascade of biological events that correspond with the etiology of the disease [40585], [172466], [227586], [265997], [273648], [291135]. VX-745 has recently emerged as a novel inhibitor of p38 MAPK with anti-inflammatory actions [214928], [291135], [372054]. Therefore, targeting this pathway as a potential therapeutic strategy in combating the pathology and progression of RA, thereby suppressing the downstream inflammatory cytokine pathways [210221], [212641], [230354], [237661], [237695], [237696], [239570], [254168], appears very appropriate and, perhaps, very rewarding given the promising insights into its novel actions [372054], [372943].

Despite the fact that VX-745 recently began phase II clinical trials, more data have yet to emerge to be able to fully screen the efficacy of the drug in ameliorating RA. Should the effects of the inhibitor in suppressing the inflammatory process before and during the evolution of RA prove to be effective and manipulative, the effort is worthy and appropriate in strategically defining the next steps that should be undertaken in order to eradicate the potential harmful effects of the disease. Perhaps examining, more specifically, the mechanisms of the anti-inflammatory action of this drug is strongly warranted, and requires accurate, objective and precise assessment of the onset, evolution and the complications associated with the pathophysiology of RA.

Development history

Developer	Country	Status	Indication	Date	Reference
Vertex Pharmaceuticals Inc	Western Europe	C2	Rheumatoid arthritis	03-NOV-99	346067
Vertex Pharmaceuticals Inc	USA	C2	Rheumatoid arthritis	03-NOV-99	386727
Kissei Pharmaceutical Co Ltd	Western Europe	C2	Rheumatoid arthritis	24-OCT-00	346067
Kissei Pharmaceutical Co Ltd	Japan	DX	Inflammation	15-MAR-01	401955
Kissei Pharmaceutical Co Ltd	Japan	DX	Neurological disease	15-MAR-01	401955

Development history (continued)

Developer	Country	Status	Indication	Date	Reference
Vertex Pharmaceuticals Inc	Europe	DX	Inflammation	15-MAR-01	401955
Vertex Pharmaceuticals Inc	Europe	DX	Neurological disease	15-MAR-01	401955
Vertex Pharmaceuticals Inc	USA	DX	Inflammation	15-MAR-01	401955
Vertex Pharmaceuticals Inc	USA	DX	Neurological disease	15-MAR-01	401955

Literature classifications

Biology

Study Type	Effect Studied	Experimental Model	Result	Reference
In vitro	Crystal structure of p38 MAPK	*Spodoptera frugiperda* (Sf9) insect cells (ATCC)	The three-dimensional structure of p38 MAPK at 2.3 Å resolution.	224121
In vitro	Inhibition of inflammatory cytokines.	PBMCs.	IL-1β (IC_{50} = 56 nM); TNFα (IC_{50} = 52 nM).	369960 371548 395083
In vitro	Inhibition of inflammatory mediators.	PBMCs.	Blockading LPS-stimulated production of IL-1β and TNFα; IL-6 and IL-8 production induced by TNFα and IL-1; and COX-2 synthesis mediated by LPS and IL-1β.	408713
In vitro	Inhibition of inflammatory cytokines.	Human whole blood assay.	IL-1β (IC_{50} = 152 nM); TNFα (IC_{50} = 177 nM).	369960 371548
In vivo	Suppression of paw inflammation.	Classical cartilage-induced arthritis model in the mouse.	VX-745 (10 mg/kg bid) produced a 33.1% suppression of paw inflammation, equivalent to maximum effect using prednisolone.	372054 372943
In vivo	Attenuation of AA.	Rat.	Effectiveness in AA with an ED_{50} = 5 mg/kg bid, indicated by measuring ankle joint diameter.	372054 372943 395083
In vivo	Attenuation of bone resorption and inflammation.	Rat.	Histological scores were 93% inhibition for bone resorption and 56% inhibition of inflammation.	395083
In vivo	Attenuation of severity of disease.	Mouse CIA model.	VX-745 (50 mg/kg bid) administered in propylene glycol vehicle produced a dose-responsive decrease in severity score.	369960

Metabolism

Study Type	Effect Studied	Experimental Model	Result	Reference
In vivo	Pharmacokinetics.	Rats (n = 3).	VX-745 (40 to 43 mg/kg bid po) was administered in an isopropanol vehicle. Absolute bioavailability data and $t_{1/2}$ values of 56% and 4.5h, respectively.	395083
In vivo	Pharmacokinetics.	Rat adjuvant arthritis model.	VX-745 (5 mg/kg po bid) produced a 54% protection against arthritis with oral bioavailability.	371548

Clinical

Effect studied	Experimental model	Result	Reference
Pharmacokinetics and tolerability.	Healthy volunteers given escalating doses of VX-745.	Inhibition of experimentally induced TNFα production using specific biochemical assays with blood samples.	317656
Pharmacokinetics and pharmacodynamics.	10 Patients with RA.	The activity of VX-745 was assessed and clinical disease activity markers were monitored.	346067
Pharmacodynamics and tolerability in monotherapy.	135 Adult patients with RA.	The clinical activity was evaluated with escalating doses of VX-745, evaluating objective clinical response rates, self-reported patient health assessments and pharmaco-dynamic markers of drug activity.	395083 399818

Associated patent

Title Substituted nitrogen containing heterocycles as inhibitors of p38 protein kinase.

Assignee Vertex Pharmaceuticals Inc

Publication WO-09827098 25-JUN-98

Priority US-00034288 18-DEC-96

Inventors Bemis GW, Salituro FG, Duffy JP, Cochran JE, Harrington EM, Murcko MA, Wilson KP, Su M, Galluio VP.

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